REMARKS

Status of the Claims

Claims 3, 9, 17, 23, and 31 have been canceled without prejudice to or disclaimer of the subject matter contained therein. Claims 1, 8, 16, 22, and 30 have been amended to recite "biologically active" IFN- β. Support for this amending language can be found throughout the specification, for example, on page 10, lines 1-17. Additionally, claims 1, 8, 16, 22, and 30 have been amended to include the limitations of claims 3, 9, 17, 23, and 31, respectively. Claims 10 and 24 have been amended solely to correct dependency. No new matter has been added by way of any claim amendments.

These claim amendments were not presented earlier as Applicants earnestly believed that the previously presented claims recited patentable subject matter. Pursuant to 37 C.F.R. § 1.116 and the *Manual of Patent Examining Procedure* (MPEP), any amendment that will place the application in condition for allowance may be entered after final rejection (MPEP § 714.12). Applicants believe that this amendment places claims 1, 2, 4-8, 10-16, 18-22, 24-30, and 32-35 in condition for allowance. The Examiner is respectfully requested to enter these claim amendments to further prosecution or to place the application in better condition for appeal.

Claims 1, 2, 4-8, 10-16, 18-22, 24-30, and 32-35 are pending in the present application. Reexamination and reconsideration of the claims are respectfully requested. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Enablement

Claims 1-35 remain rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement of Section 112. Specifically, the Examiner asserts that the claims can be interpreted as reading on any fragment of an IFN-β polypeptide or any polypeptide with at least 80% sequence identity to SEQ ID NO:1, and are therefore drawn to an excessive number of potential polypeptides because the claims do not require any function for the polypeptides. Claims 3, 9, 17, 23, and 31 have been canceled, rendering this rejection moot as

applied to these claims. This rejection is respectfully traversed as applied to claims 1, 2, 4-8, 10-16, 18-22, 24-30, and 32-35.

Although Applicants maintain that the claims as originally filed complied with the enablement requirements, independent claims 1, 8, 16, 22, and 30 have been amended to include a limitation that the recited IFN- β is "biologically active." Support for this amending language can be found throughout the specification, for example, on page 10, lines 1-17. Assays to determine whether IFN-β variants encompassed by the invention retain biological activity (*e.g.*, the ability to bind to IFN-β receptors) are routine to one of skill in the art. See, for example, the extensive listing of references found in the specification on page 10, lines 1-8, all of which were well known in the art prior to the filing of the present application.

As previously made of record in Applicants' reply to the Office Action of October 5, 2006 (dated February 5, 2007), variants of IFN-β were well known to those of skill in the art at the time the present application was filed (see, *e.g.*, page 10, lines 9-17 of the specification, which includes more than 30 non-limiting examples of IFN-β variant polypeptides encompassed by the invention). Further to the Examiner's request, Applicants provide herewith sequence alignments comparing the IFN-β sequences cited on page 10, lines 9-17 of the specification with the IFN-β sequence set forth in SEQ ID NO:1. The table below lists 32 IFN-β variants (the parenthetical number is the number assigned for the alignment), indicates their percent sequence identity to SEQ ID NO:1 and includes the reference for each variant. Sequence alignments were performed using the ALIGN program (version 2.0) with a PAM 120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. Percent sequence identity ranges from 77.2% (IFNX410) to 99.4% (IFN-β_{ser17}, IFNX444 and IFNX445). The complete alignments are attached as **Appendix A**.

IFN-β variant	Percent sequence identity	Reference
IFN-β_{ser17} (No.1)	99.4	U.S. Patent No. 4,518,584
IFNX412 (No.2)	97.0	U.S. Patent No. 4,738,844
IFNX413 (No.3)	96.4	U.S. Patent No. 4,738,844
IFNX414 (No.4)	97.0	U.S. Patent No. 4,738,844
IFNX421 (No.5)	86.8	U.S. Patent No. 4,738,844
IFNX401 (No.6)	97.0	U.S. Patent No. 4,738,844

IFN-β variant	Percent sequence identity	Reference
IFNX423 (No.7)	88.0	U.S. Patent No. 4,753,795
IFNX429 (No.8)	88.0	U.S. Patent No. 4,753,795
IFNX405 (No.9)	94.0	U.S. Patent No. 4,753,795
IFNX416 (No.10)	93.4	U.S. Patent No. 4,769,233
IFNX417 (No.11)	97.0	U.S. Patent No. 4,769,233
IFNX418 (No.12)	96.4	U.S. Patent No. 4,769,233
IFNX430 (No.13)	94.0	U.S. Patent No. 4,769,233
IFNX444 (No.14)	99.4	U.S. Patent No. 4,769,233
IFNX445 (No.15)	99.4	U.S. Patent No. 4,769,233
IFNX446 (No.16)	98.8	U.S. Patent No. 4,769,233
IFNX447 (No.17)	94.0	U.S. Patent No. 4,769,233
IFNX448 (No.18)	93.4	U.S. Patent No. 4,769,233
IFNX449 (No.19)	93.4	U.S. Patent No. 4,769,233
IFNX456 (No.20)	94.0	U.S. Patent No. 4,769,233
IFNX485 (No.21)	94.0	U.S. Patent No. 4,769,233
IFNX407 (No.22)	80.2	U.S. Patent No. 4,793,995
IFNX408 (No.23)	94.6	U.S. Patent No. 4,793,995
IFNX409 (No.24)	94.0	U.S. Patent No. 4,793,995
IFNX410 (No.25)	77.2	U.S. Patent No. 4,793,995
IFNX415 (No.26)	91.7	U.S. Patent No. 4,793,995
IFNX402 (No.27)	80.2	U.S. Patent No. 4,793,995
IFNX419 (No.28)	85.0	U.S. Patent No. 4,793,995
IFNX420 (No.29)	89.8	U.S. Patent No. 4,793,995
IFNX404 (No.30)	95.2	U.S. Patent No. 4,793,995
IFNX403 (No.31)	81.4	U.S. Patent No. 4,793,995
IFNX406 (No.32)	77.8	U.S. Patent No. 4,793,995

To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir. 1999); *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *PPG Inds., Inc. v. Guardian Inds. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495-96, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). "That some experimentation may be required is not fatal, the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444. The enablement section of 35 U.S.C. § 112, first paragraph,

"requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (C.C.P.A. 1970). In order to determine whether the present claims are enabled, an analysis of the teachings of the specification must be performed as well as an inquiry into the knowledge of persons of ordinary skill in the art. *In re Bowen*, 492 F.2d 859, 861, 181 USPQ 48, 50 (C.C.P.A. 1974).

Applicants respectfully submit that there is a vast amount of supporting evidence in the field of IFN-β molecular biology, which is also supported by the disclosure of the present application, on how to routinely make and use *biologically active* variants of IFN-β. Additionally, as shown in the table above, sequence alignments comparing the IFN-β sequences cited on page 10, lines 9-17 of the specification with the IFN-β sequence set forth in SEQ ID NO:1 show that they share at least 80% sequence identity. Therefore, the enablement rejection should be withdrawn.

Written Description

Claims 1-35 remain rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement of Section 112. Specifically, the Examiner maintains that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. Claims 3, 9, 17, 23, and 31 have been canceled, rendering this rejection moot as applied to these claims. This rejection is respectfully traversed as applied to claims 1, 2, 4-8, 10-16, 18-22, 24-30, and 32-35. As discussed above, although Applicants maintain that the claims as originally filed complied with the written description requirements, independent claims 1, 8, 16, 22, and 30 have been amended to include a limitation that the recited IFN- β is "biologically active."

In order to satisfy the written description requirement of 35 U.S.C. § 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Every species encompassed by the

claimed invention, however, need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding In.*, 230 F.3d 1320 1323, 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims.").

Moreover, the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" state that a genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." 66 Fed. Reg. 1106 (January 5, 2001). This is in accordance with the standard for written description set forth in *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel* 984 F.2d 1164 (Fed. Cir. 1993).

The claims of the present application meet the requirements for written description set forth by the Federal Circuit. As discussed herein, there is a vast amount of supporting evidence in the field of IFN-β molecular biology, which is also supported by the disclosure of the present application, on how to routinely make and use *biologically active* variants of IFN-β. Assays to determine whether IFN-β variants encompassed by the invention retain biological activity, such as the ability to bind to IFN-β receptors, are routine in the art (see, *e.g.*, the extensive listing of references found in the specification on page 10, lines 1-8). Additionally, as shown in the table above, sequence alignments comparing the IFN-β sequences cited on page 10, lines 9-17 of the specification with the IFN-β sequence set forth in SEQ ID NO:1 show that they share at least 80% sequence identity.

Clearly the skilled artisan would recognize that Applicants were in possession of the claimed invention at the time of filing and the requirements of 35 U.S.C. § 112, first paragraph,

have been satisfied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 8-35 remain rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Arora *et al.* (*J. Biotech.* 52:127-33, 1996) in view of Dorin *et al.* (U.S. Patent No. 5,814,485). Claims 9, 17, 23, and 31 have been canceled, rendering this rejection moot as applied to these claims. This rejection is respectfully traversed as applied to claims 8, 10-16, 18-22, 24-30, and 32-35.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), set out the framework for applying the statutory language of Section 103:

1. Determining the scope and content of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering any relevant secondary considerations.

Arora *et al.* teach a method for isolating IFN-γ from *E. coli* inclusion bodies, including solubilization of the inclusion bodies in guanidine HCl, renaturation of the solubilized protein mixture by dilution in a refolding buffer, dialysis of the renatured protein mixture against a second buffer, and purification of the IFN-γ following loading of the resulting solution on a S-Sepharose column. Dorin *et al.* teach methods of recombinant production of IFN-β and its subsequent purification, and disclose various excipients that can be included in IFN-β formulations having a pH of about 6.0 to 7.5.

Applicants have discovered methods for preparing IFN-β, including denaturing IFN-β by dissolving IFN-β in guanidine HCl followed by renaturation via dilution into a first buffer. In some embodiments the renatured IFN-β is substantially monomeric. In still other embodiments, the renatured IFN-β is diafiltered or dialyzed into a second buffer to remove residual guanidine HCl. As the Examiner has acknowledged, "neither Arora nor Dorin teach buffers in the claimed pH range, and specific concentrations of guanidine HCl" (Office Action mailed April 30, 2007, page 6, lines 26-27). To advance prosecution, Applicants have amended independent claims 8,

16, 22, and 30 to include the limitations of specific pH ranges/specific concentrations of guanidine HCl, as found in original claims 9, 17, 23, and 31, respectively.

The Examiner's rationale for maintaining the rejection of claims 8-35 under 35 U.S.C. § 103(a) is that "the teachings of Arora highlight the fact that protein isolation using guanidine HCl was known in the art at the time the instant invention was filed, while Dorin shows that the protein of SEQ ID NO:1 was also known at the time the instant invention was filed …. Thus, one of ordinary skill in the art would know of a method of protein purification that promotes protein refolding … and would therefore be motivated to use this method to purify the therapeutically useful protein of Dorin" (Office Action, page 6, lines19-25). Applicants respectfully disagree with this assertion. In a list of **critical** variables to be considered in protein refolding, Fiona *et al.* (In *Guide to Protein Purification*, ed. by Deutscher, MP., Ch. 20, Academic Press, Inc., 1990, pp. 264-76; copy provided as Exhibit A in the response mailed on February 5, 2007) place pH at the top of the list (see page 270, emphasis added). Accordingly, Applicants submit that substantial differences exist between the disclosure of Arora *et al.* regarding a method for isolating IFN-γ from *E. coli* inclusion bodies, which lacks critical teachings concerning pH ranges and specific concentrations of residual guanidine HCl, and the methods recited in pending claims 8, 10-16, 18-22, 24-30, and 32-35 for preparing IFN-β.

As the Supreme Court has recently made clear, in an obviousness analysis under § 103 a demonstration of some teaching, suggestion or motivation to combine the prior art provides a "helpful insight." *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350, slip op. at 14 (U.S. Apr. 30, 2007). In the instant case, Applicants submit that no such helpful insight exists. Contrary to the Examiner's assertions, nothing in Arora *et al.* or Dorin *et al.* would have provided a reason for the skilled artisan to combine their teachings to arrive at Applicants' methods for preparing IFN-β. At most one of skill in the art would view the combination of these two references as an invitation to experiment with multiple parameters (*e.g.*, different buffers with different pHs) to ascertain their suitability in methods for preparing IFN-β. Yet an invitation to experiment is not sufficient grounds to reject an invention as obvious. One of skill in the art at the time of the invention would not have had sufficient guidance to have a reasonable expectation of success in combining the teachings of Arora *et al.* with Dorin *et al.* to arrive at Applicants' claimed

invention. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90-91 (Fed. Cir. 1986).

Claims 1-7 remain rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over van Oss (*J. Protein Chem.* 8:661-68) in view of Arora *et al.* and further in view of Dorin *et al.* Claim 3 has been canceled, rendering this rejection moot as applied to this claim. This rejection is respectfully traversed as applied to claims 1, 2 and 4-7.

van Oss discusses the well known technique of protein precipitation with ethanol. As discussed above, Arora *et al.* teach a method for isolating IFN-γ from inclusion bodies and Dorin *et al.* teach methods of recombinant production of IFN-β and its subsequent purification. Applicants have discovered methods for preparing IFN-β, including precipitating IFN-β using an alcohol, dissolving the IFN-β precipitate in guanidine HCl followed by renaturation via dilution into a first buffer, and diafiltration or dialysis of the renatured IFN-β into a second buffer to remove residual guanidine HCl. As previously noted, the Examiner has acknowledged that "neither Arora nor Dorin teach buffers in the claimed pH range, and specific concentrations of guanidine HCl" (Office Action, page 6, lines 26-27). This deficiency is not remedied by the teachings of van Oss. To advance prosecution, Applicants have amended independent claim 1 to include the limitations of a specific pH range and specific concentration of guanidine HCl, as found in original claim 3.

The Examiner's rationale for maintaining the rejection of claims 1-7 under 35 U.S.C. § 103(a) is that "van Oss, by teaching that ethanol precipitation of proteins is a method of protein isolation/purification that is well-known in the art, provides the motivation to precipitate IFN-β using an alcohol such as ethanol" (Office Action, page 7, lines 19-21). Applicants respectfully disagree with this assertion. As previously discussed, in a list of **critical** variables to be considered in protein refolding, Fiona *et al.* (In *Guide to Protein Purification*, ed. by Deutscher, MP., Ch. 20, Academic Press, Inc., 1990, pp. 264-76) place pH at the top of the list (see page 270, emphasis added). Accordingly, Applicants submit that substantial differences exist between the disclosure of Arora *et al.* regarding a method for isolating IFN-γ from *E. coli* inclusion

bodies, which lacks critical teachings concerning pH ranges and specific concentrations of residual guanidine HCl, and the methods recited in pending claims 1, 2 and 4-7 for preparing IFN-β.

Furthermore, Applicants submit that nothing in van Oss remedies the lack of motivation to combine Arora *et al*. and Dorin *et al.*, as discussed above. The mere fact that the different elements of an invention may be disclosed in the prior art is insufficient to establish obviousness without a motivation to combine the prior art references. Accordingly, a showing by van Oss that ethanol precipitation of proteins is a common and effective procedure for protein isolation is insufficient to render the present claims obvious. As noted by the Federal Circuit:

> Most if not all inventions arise from a combination of old elements. Thus, every element of a claimed invention may often be found in the prior art. However, identification in the prior art of each individual part claimed is insufficient to defeat the patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab* 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (internal citations omitted).

In the present case, the cited references lack any suggestion or motivation to combine their teachings to arrive at the methods for preparing IFN-β discovered by Applicants. As discussed above, the combination of the references at best is an invitation to one of skill in the art to perform additional experiments. However, an invitation to experiment is not sufficient grounds to reject an invitation as obvious.

In view of the above amendments and arguments, Applicants contend that a *prima facie* case of obviousness under 35 U.S.C. § 103(a) has not been established. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §§ 112 and 103 are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned attorney.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/david e.cash/

David E. Cash
Registration No. 52,706

Customer No. 45853 **ALSTON & BIRD LLP** Bank of America Plaza 101 South Tryon Street, Suite 4000 Charlotte, NC 28280-4000 Tel Raleigh Office (919) 862-2200 Fax Raleigh Office (919) 862-2260	**ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON JULY 2, 2007.**